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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/513,024 02/25/00 VILEN

B 2879-64

EXAMINER

HM12/1031

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ROARK, J

ART UNIT

PAPER NUMBER

1644

DATE MAILED:

10/31/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

**Advisory Action**

Application No.

09/513,024

Applicant(s)

VILEN ET AL.

Examiner

Jessica H. Roark

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 12 October 2001 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

**PERIOD FOR REPLY** [check either a) or b)]

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
- b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on \_\_\_\_\_. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
- (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
- (b) ☐ they raise the issue of new matter (see Note below);
- (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
- (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: \_\_\_\_\_

3. ☐ Applicant's reply has overcome the following rejection(s): \_\_\_\_\_.
4. ☐ Newly proposed or amended claim(s) \_\_\_\_\_ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: Please see attached.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: \_\_\_\_\_

Claim(s) objected to: \_\_\_\_\_

Claim(s) rejected: 1, 4-6, 9, 10, 18, 19, 21, 22, 30, 31 and 33.Claim(s) withdrawn from consideration: 12-14, 20 and 32.

*Phillip Gambel*  
PHILLIP GAMBEL, PH.D  
PRIMARY EXAMINER  
*TECH CENTER 1600*  
*10/30/01*

8. ☐ The proposed drawing correction filed on \_\_\_\_\_ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). \_\_\_\_\_.
10. ☒ Other: Notice of references cited attached

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1. The text of those sections of Title 35 USC not included in this Action can be found in a prior Action. This Office Action will be in response to applicant's arguments, filed 10/12/01 (Paper No. 17). The rejections of record can be found in previous Office Actions (Paper Nos. 12 and 16).

2. Claims 1, 4-6, 10, 18 and 33 stand rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al. (Int. J. Hematol. 1996 64:39-46, of record, see entire document).

Applicant's arguments, filed 10/12/01 (Paper No. 1) have been fully considered with respect to the instant claims, but have not been found convincing, essentially for the reasons of record.

Applicant argues that the teachings of Nakamura et al., taken as a whole, do not support that the anti-CD79b (anti-Ig $\beta$ ) antibody used in the methods of Nakamura et al. induced receptor desensitization. Applicant points to the results in Figure 3, showing that anti-CD79b treatment was unable to prevent stimulation of B cells by anti-IgM. Applicant further refers the Examiner to the Discussion in which Nakamura et al. teach that the anti-CD79b antibody could not induce B cell unresponsiveness (e.g., page 44). Applicant again points the Examiner to page 43, where Nakamura et al. set forth three possible mechanisms of anti-CD79b action. Finally, Applicant points to the conclusion of Nakamura et al. on page 45, the bridging paragraph between columns 1 and 2 wherein Nakamura et al. conclude that (in the experiment previously referenced by the Examiner) the "inhibitory effect is caused by down-modulation of BCR and inhibition of B lymphocyte differentiation, and not by induction of B lymphocyte unresponsiveness". While Applicant acknowledges that Nakamura et al. teach the suppression of B cell responses, Applicant again asserts that the suppressive effect is likely due to a *stimulatory* effect of the anti-CD79b antibody.

As previously noted in Paper Nos. 12 and 16, Nakamura et al. teach contacting a B cell receptor (BCR) with an antibody to the transducer component CD79b (see entire document, e.g., "Abstract"). In addition, the antibody of Nakamura et al. is a divalent antibody; the extracellular binding component of the receptor comprises IgD or IgM (e.g., Figure 2); and the antibody is contacted with the receptor in an *in vitro* assay (e.g., "Methods"). Nakamura et al. in their "Discussion" on pages 43-45 clearly consider the anti-CD79b antibody to be an effective suppressant of B cell responsiveness.

The Examiner acknowledges that Nakamura et al. teach that their *in vitro* experiments did not result in B cell "unresponsiveness" (e.g. in the bridging paragraph of columns 1 and 2 on page 45). However, *the instant claims do not recite a limitation requiring that unresponsiveness be induced in the B cells*, rather, the instant claims require that contact with the antibody causes a dissociation or inhibits association of extracellular ligand binding component (mIg) and the transducer component (which comprises CD79b/Ig $\beta$ ).

The recited method and that of Nakamura et al. employ what appears to be the same product – an antibody to the CD79b/ Ig $\beta$  component of the BCR transducer complex. The instantly recited methods recite properties inherent to contacting a BCR with that product. While the Examiner recognizes that the nature of the BCR can vary depending upon the developmental/activation state of the B cell expressing it, the instant claims also do not include any limitations with respect to the nature of the BCR.

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Neither do the instant claims recite a particular assay system and result that can be used to differentiate the teachings of Nakamura et al. from the instant methods. It is further noted that the pathway involved in transmitting either a stimulatory or inhibitory signal via the BCR is complex, and that there are many different readouts used in the experimental literature to assay the effect of different agents on this pathway. These assays include those in which different effects at various points along the signaling pathway itself are assayed (e.g., calcium flux, phosphorylation or dephosphorylation of various components of the pathway, the formation of inositol trisphosphate or diacylglycerol, etc.), and also include readouts of the consequence of activation/inhibition of the pathway (proliferation and differentiation of the B cell into antibody secreting cells). (See for example the brief summary provided in Sections 3-24 and 3-25 of Chapter 3 of "IMMUNOBIOLOGY: The Immune System in Health and Disease", Janeway and Travers eds, 3<sup>rd</sup> edition, 1997, Current Biology Ltd/Garland Publishing Inc.).

Nakamura et al. teach that the anti-CD79b antibody was inhibitory in at least one *in vitro* assay, the production of antibody (e.g., Figure 4). Applicant asserts that this is due to a stimulatory effect of the antibody of Nakamura et al., however no objective evidence to substantiate this assertion is provided. The Examiner also notes that although the claims recite that the antibody "does not substantially stimulate the receptor", there does not appear to be a definition provided in the instant specification that would allow one of ordinary skill in the art to determine that an antibody did not "substantially stimulate the receptor". In view of the inhibition of the antibody response demonstrated in Figure 4 of Nakamura et al., representing a readout of the downstream events of BCR signaling as noted supra and previously, the evidence of record indicates that, *at least in the culture conditions associated with Figure 4*, the anti-CD79b antibody of Nakamura et al. does not substantially stimulate the BCR. Consequently, the teachings of Nakamura et al. appear to anticipate the instant invention.

*Applicant is invited to provide objective evidence that there is a patentable distinction between the teachings of Nakamura et al and the instant invention.* It is noted that Applicant shows that two anti-CD79b/Ig $\beta$  antibodies do not substantially stimulate the BCR by providing data that these antibodies do not induce an acute calcium flux and inhibit the calcium response after antigen stimulation in experiments presented in Example 9 on page 54 of the specification.

However, at the present time and based upon the evidence of record, there does not appear to be a patentable distinction between the claimed and referenced methods. Nakamura et al. teach the same method step of contacting a B cell antigen receptor with the same compound (anti-Ig $\beta$ /CD79b antibodies) as employed in the instant method. The CAFC recently held in Bristol-Myers Squibb Co. v. Ben Venue Laboratories Inc., 58 USPQ2d 1508 (CA FC 2001) that when a claimed process is not directed to a new use, *consists of the same steps described in a prior art reference*, and the newly discovered results of the known process *directed to the same purpose* are inherent, the process is not patentable.

Applicant is reminded that "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [or her] claimed product. Whether the rejection is based on 'inherency' under 35 U.S.C. 102, on 'prima facie obviousness' under 35 U.S.C. 103, jointly or alternatively, the burden of proof is the same...[footnote omitted]." The burden of proof is similar to that required with respect to product-by-process claims. In re Fitzgerald, 619 F. 2d 67, 70, 205 USPQ 594, 596 (CCPA 1980) (quoting In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-34 (CCPA 1977)). (See MPEP 2112.)

The rejection is maintained in the absence of evidence clearly establishing a patentable distinction between the claimed and referenced methods.

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3. Claims 1, 4-6, 9-10, 18-19, 21-22, 30-31 and 33 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Ways et al. (US Pat. No. 6,103,713, of record) in view of Nakamura et al. (Int. J. Hematol. 1996 64:39-46, of record), and in further view of Vilen et al. (J. Immunol. 1996 159:231-243, of record).

Applicant's arguments, filed 10/12/01, have been fully considered, but have not been found convincing, essentially for the reasons of record and as set forth supra.

Applicant traverses the rejection of record with respect to Nakamura et al. for the reasons set forth supra.

Applicant also again traverses the rejection of record on the grounds that there is no motivation to combine the teachings of Ways et al. with that of either Nakamura et al. or Vilen et al., in particular because Vilen et al. teaches that long-term B cell unresponsiveness is independent of the PKC activation which is blocked in the method of Ways et al.

The rejection of record may be found more fully in Paper Nos. 12 and 16,

Applicant's new arguments with respect to Nakamura et al. have been addressed supra.

Applicant's traversal with respect to the lack of motivation to combine the references appears to be the same as that previously set forth on 5/11/01.

The Examiner again notes that in the instant case (as noted previously in Paper Nos. 12 and 16), the ordinary artisan at the time the invention was made would have been motivated to substitute the antibody of Nakamura et al. for the PKC inhibitor utilized in the methods of Ways et al. for treating autoimmune diseases associated with B cell activation, including SLE, because the ordinary artisan at the time the invention was made would have recognized that the antibody of Nakamura et al. that acted upstream (proximal to the BCR) in the signal transduction pathway would be more efficacious than an inhibitor of PKC in blocking B cell activation, and because Nakamura et al. teach that antibodies to the transducer components (e.g., CD79b) would be particularly desirable for *in vivo* use. The teachings of Vilen et al. that long-term B cell unresponsiveness is independent of PKC activation provides further motivation to substitute the anti-transducer component antibody for the PKC inhibitor because, although Ways et al. teach that the PKC inhibitor does function in methods of treating autoimmune diseases such as SLE; based upon the teachings of Nakamura et al. and Vilen et al. the ordinary artisan would have expected that an antibody to the transducer component would be even more efficacious in that the antibody would provide long-term B cell unresponsiveness.

Ways et al., Nakamura et al. and Vilen et al. provide sufficient teachings that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention, even without knowledge of the detailed mechanism of action or a full characterization of the signaling cascade. Ways et al. teach a highly desirable endpoint as a functional consequence of inhibiting the BCR signaling cascade. That PKC acts downstream (distal to the BCR) in the BCR signaling cascade was well known in the art at the time the invention was made, as taught and reviewed by Vilen et al. Nakamura et al. teach the antibody to the extracellular domain of the transducer component of the BCR, and that antibodies to the transducer components would be particularly desirable for *in vivo* use in methods of suppressing humoral immunity, such as SLE.

Thus the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejection is therefore maintained, essentially for the reasons of record.

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4. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica H. Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday, 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Jessica Roark, Ph.D.  
Patent Examiner  
Technology Center 1600  
October 30, 2001

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